# PATENT COOPERATION TREATY



# PCT

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>X62428PC | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/EP2004/010996 | International filing date *(day/month/year)*<br>01.10.2004 | Priority date *(day/month/year)*<br>02.10.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>C12N9/12, A61K38/18, G01N33/50 | | |
| Applicant<br>XANTOS BIOMEDICINE AG | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 21.07.2005 | 19.09.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Stolz, B<br>Telephone No. +49 89 2399-8416 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/010996

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-29 as originally filed

**Sequence listings part of the description, Pages**

1-5 as originally filed

**Claims, Numbers**

1-15 filed with the demand

**Drawings, Sheets**

1/8-8/8 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-15 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-15 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-15 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

## Supplemental Box relating to Sequence Listing

**Continuation of Box I, item 2:**

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

1. The application discloses an effect of TBK-1 on VEGF expression. Thus TBK-1 affects angiogenesis. siRNA based on TBK-1 counteracts this effect. Second medical/diagnostic use claims are directed to a) the use of TBK-1 for the promotion of angiogenesis (claims 1 to 3), b) the use of TBK-1 for the diagnosis of a number of diseases (claim 4), c) the use of inhibitors of TBK-1 for the treatment of the diseases of claim 5. Claims 11 to 15 relate to a method of identifying anticancer drugs involving TBK-1 and testing for antiangiogenic activity.

2. Novelty and inventive step of claims 1 to 3 and 5 to 15

   An effect of TBK-1 on VEGF has not been disclosed in the cited prior art. Therefore, the subject matter of claims 1 to 3, and 5 to 15 is novel and cannot be derived from the prior art in an obvious way.

3. Novelty and inventive step of claim 4

   Claim 4 relates to the use of TBK-1 or the nucleic acid encoding TBK-1 for the diagnosis of i.a. cancer, rheumatoid arthritis, atherosclerosis or chronic inflammation. WO98/39410 discloses T2K (TBK-1) as a factor acting on IL-1 and TNF via NF-kB (p. 1). The use of T2K specific antibodies and nucleic acids in diagnosis is discussed on p. 2 (lines 10-11) and p. 5 (lines 10-15). However, this document does not sufficiently disclose any specific diagnostic use. Thus, novelty and inventive step are acknowledged for claim 4.

4. Art. 5/6 PCT (Disclosure and Clarity)

   Claim 4 relates to the use of TBK-1 as a diagnostic agent. While the description discloses the use of antibodies recognizing TBK-1 as a diagnostic tool, it is not immediately obvious how one should use the protein itself as a diagnostic agent.

   While the application provides an example of an siRNA, there is no disclosure of an aptamer and creating one without any specific technical teaching is considered an undue burden. Furthermore, there are two examples of low Mw compounds but this is insufficient to support a claim 8 directed to the use of any low Mw inhibitor of

whatever structure.

PCT/EP2004/010996
Xantos Biomedicine AG

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## Claims

1. Use of a nucleic acid encoding TBK-1 or a functional active derivative thereof for the preparation of a pharmaceutical composition for the treatment of ischemic or dental diseases, smoker's leg and diabetic ulcers or for the stimulation of wound healing.

2. The use of claim 1, wherein the nucleic acid induces the production of VEGF.

3. The use according to any of claims 1 or 2, wherein the nucleic acid induces the formation of vascular vessels.

4. Use of

a) TBK-1,
b) a functional active derivative thereof,
c) a nucleic acid encoding TBK-1, and /or
d) means for the detection of the molecules of sections a), b) , c) or d)

for the preparation of a diagnostic agent for the diagnosis of ischemic or dental diseases, smoker's leg and diabetic ulcers, wound healing disorders, cancer, hyperplasia, tumor progression, rheumatoid arthritis, psoriasis, artherosclerosis, retinopathy, osteoarthritis, endometriosis or chronic inflammation.

5. Use of a TBK-1 inhibitor for the preparation of a pharmaceutical composition for inhibiting or reducing angiogenesis in the treatment of cancer, hyperplasia, rheumatoid arthritis, psoriasis, artherosclerosis, retinopathy, osteoarthritis, endometriosis or chronic inflammation.

6. The use of claim 5, wherein the inhibitor inhibits the production of VEGF.

7. The use of any of claims 5 or 6, wherein the inhibitor inhibits the formation of vascular vessels.

8. The use of any of claims 5 or 7, wherein the inhibitor is selected from the group consisting of antisense oligonucleotides, antisense RNA, siRNA, aptamers and Low molecular weight molecules (LMWs).

9. The use of claim 8, wherein the LMWs bind to the ATP-binding site of the kinase domain of TBK-1.

10. The use of any of claims 4 to 9, wherein the disease is cancer, preferably selected from the group consisting of brain cancer, pancreas carcinoma, stomach cancer, colon carcinoma, skin cancer, especially melanoma, bone cancer, kidney carcinoma, liver cancer, lung carcinoma, ovary cancer, mamma carcinoma, uterus carcinoma, prostate cancer and testis carcinoma.

11. A method for the identification of an anti-cancer drug, wherein

a) a potential TBK-1 interactor is brought into contact with TBK-1 or a functional derivative thereof, and

b) binding of the potential interactor to TBK-1 or the functional derivative thereof is determined, and

c) the anti-angiogenic capacity of the potential interactor is determined.

12. The method of claim 11, wherein the anti-angiogenic capacity is determined by measuring the inhibition of VEGF production.

13. The method of any of claims 11 or 12, wherein the potential interactor is provided in the form of a chemical compound library.

14. The method of claim 13, wherein the chemical compound library consists of a group of molecules or substances that bind to the ATP binding site of the kinase domain of TBK-1.

15. The method of any of claims 11 or 14, wherein the method is carried out on an array.